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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/832,069
Filing Date: April 10, 2001
Appellant(s): RUNGE ET AL.

09/832,069
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed May 8, 2006 appealing from the Office action mailed April 5, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Exhibit 1 -- Corral-Debrinski et al. article; made of record by the Examiner in the Office Action dated February 15, 2005, at page 4;

Exhibit 2 - Lenaz article; made of record by Appellants in their Amendment and Response dated January 20, 2006 at page 4;

Exhibit 3 -- Hudson et al. article; made or record by Appellants in their Amendment and Response dated January 20, 2006 at page 4; and

Exhibit 4 – Williams et al. article; made of record by Appellants in their Amendment and Response dated January 20, 2006 at page 5 (also submitted as reference (248; PTO 1449; July I , 2005)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for measuring the amount of oxidative stress in an individual by detecting the amount of DNA damage per length of DNA using QPCR, does not reasonably provide enablement for detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to a method for measuring the amount of oxidative stress in an individual by detecting the amount of DNA damage per length of DNA using QPCR, detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state.

The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches that tissue ischemia, OXPHOS gene defects, environmental toxins, mtDNA mutations, decreased cellular ATP and oxygen radical formation all affect oxidative phosphorylation dysfunction which leads to tissue degeneration and cell death (Corral-Debrinski et al. 1992). The art does not teach how the amount of mtDNA damage is affected or associated by each of these factors.

Guidance in the Specification.

The specification states "a person having ordinary skill in this art would recognize that measurement of mitochondrial DNA damage is only one potential method to determine oxidative stress. Any downstream or resultant effect of mitochondrial DNA damage will reflect the same disease process. For example, measurement of mitochondrial protein production, changes in mitochondrial ATP production would accomplish the same goal. The specification provides no evidence teachings regarding the relationship between mtDNA damage and mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. The specification does not teach how these measurements are associated. A mutation in mtDNA may cause such problems with the mtDNA damage that there is no protein production, for example. Thus, measuring protein production of zero due to a truncation mutation would not provide any guidance of the quantity of DNA damage. Since only one mutation may completely negate the protein production, it is unpredictable that this would provide the skilled artisan with the amount of mtDNA damage present. Alternatively, the lesions or mutations/damage may occur in non-coding regions which do not affect protein. The specification has not taught that there is any direct tie. Similarly, the specification does not provide any links between mitochondrial mRNA production, mitochondrial oxidative

phosphorylation, mitochondrial ATP production or mitochondrial redox state. Reduced ATP could be a single lesion and not due to a larger number of quantitative lesions in the genome. The knockout of mitochondrial enzyme with a single mutation could cause dysfunction.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try.

Working Examples

The specification has no working examples of measuring the *amount* of mtDNA damage in tissue using mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied. As discussed above, there is no guidance or teachings in the specification how measurements of the amount of mtDNA damage in a tissue is associated with mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. There are many other factors which would affect each of theses quantities which may not be related to amount of mtDNA damage. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the specification and the art does not teach how the amount of mtDNA in a tissue may be associated with mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 8-9, and 14-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 6, 8-9, and 14-23 are indefinite because it is unclear whether the final clause of the method is directed to detecting amount of damage or mere presence of damage. The claim states, "wherein such damage is indicative of oxidative stress in said individual." Thus, the claim does not particularly appear to require establishing a correlation based upon any amount or ratio or other measurement of quantity of damage.

(10) Response to Argument

Response to Enablement Arguments

The Appellant traverses the rejection.

The Appellant states that the real enablement question is whether one of skill in the art can carry out the assay as claimed. This argument has been thoroughly reviewed, however, the claims are drawn to a method of measuring the amount of oxidative stress. The claims require that the amount of damage is indicative of oxidative stress. Thus, the skilled artisan must understand and be able to take the amount of mtDNA damage and make an assessment about the amount of oxidative stress. This is more than merely measuring mtRNA production, for example as suggested by the response. The skilled artisan must first assess the amount of mtDNA using mtRNA production, mt protein production, mt oxidative phosphorylation, mt ATP production or changes in redox state and then determine the amount of oxidative stress.

The Appellent argues that the Action takes the position that that the relationship between mitochondrial ("mt") DNA damage is not quantitatively related to mt mRNA production, mt protein production, mt oxidative phosphorylation, mt ATP production or changes in oxidative redox state, and yet provides no support for this conclusion. This argument has been thoroughly reviewed, but not deemed persuasive because there is no evidence on the record to demonstrate how the mt mRNA production, mt protein production, mt oxidative phosphorylation, mt ATP production or changes in oxidative redox state are related to mtDNA damage.

The Appellant asserts that the art does teach how the amount of mtDNA damage is affected or associated with each of the factors in question. The Appellant cites articles including Corral-Debrinki, Lenaz, Hudson and Williams.

The Appellant states that Corral-Debrinski et al. itself states "[t]his cumulative mtDNA damage was associated with a compensatory 3.5-fold induction of nuclear OXPHOS gene mRNA" and goes on to report a correlation between oxidative stress and elevated mitochondrial damage. This argument has been reviewed but not convincing because Corral-Debrinski teaches a correlation between nuclear mRNA production and does not discuss mt mRNA production, mt protein production, mt oxidative phosphorylation, mt ATP production or changes in oxidative redox state. Corral- Debrinski however teaches that the close proximity of the mtDNA to hydroxyl radicals in the inner mitochondrial membrane and the deficiency in the mtDNA repair system result in preferential oxidative damage to the mtDNA (page 170, col. 2, last paragraph). A thorough reading of Corral-Debrinski does not provide any indication that

mtDNA damage, which they study the DNA extensively, is associated with mt mRNA production, mt protein production, mt oxidative phosphorylation, mt ATP production or changes in oxidative redox state. Corral-Debrinski on the other hand appeared to state that mtDNA is in close proximity and thus would be preferentially oxidative damaged.

The Appellant asserts that the Lenaz article teaches a vicious cycle however, the "vicious cycle" in Lenaz does not provide any guidance into how the mtDNA encoded protein is indicative of oxidative stress in an individual, as required by the instant claims. Moreover, the "vicious cycle does not appear to contain information regarding detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state.

Furthermore, Hudson does not provide any guidance into how mtDNA damage may contribute to a decline in the rate of mitochondrial protein synthesis. Hudson teaches "a decrease in mitochondrial cytochrome c oxidase (COX) activity associated with a reduction in COX gene and protein expression and a similar decrease in the rate of mitochondrial protein synthesis. Damage to mitochondrial DNA *may* contribute to this decline. However, Hudson does not appear to contain information regarding detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. Hudson acknowledges the relatively few reports regarding occurrence of mtDNA damage and suggests a comprehensive and long-ranged study to determine the true impact. Thus, the teachings of Hudson does not appear to fill the gap in information regarding how the different measurements are associated and/or indicative of oxidative stress.

The last article cited is Williams which is directed to "altered mitochondrial function". Upon review of Williams, the article similarly does not contain information regarding detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state.

The Appellant asserts that the action fails to set forth evidence of unpredictability. Based upon both lack of teachings in the specification, the lack of teachings in the art prior to the filing date, the examiner has based the determination of unpredictability. The lack of art that provides a correlation is evidence of the lack of guidance provided in the art. The examiner and the Appellant appear both to have searched the art for the correlation, but do not appear to have any evidence to indicate an association regarding detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state.

The Appellant changes the enablement question from whether "one of skill in the art can carry out the assay as claimed" (page 5 of Brief) to now "whether the assay is reasonably predictive of mtDNA damage" (page 8). The examiner agrees with the second question as the true question of enablement in the instant application. The question of whether one of skill in the art can reasonably predict mtDNA damage given mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. The instant specification teaches how to measure mt protein synthesis, mt oxidative

phosphoylation as discussed in the Brief (see page 8). The specification nor the art however teaches whether mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state are reasonably predictive of mtDNA damage and what type of correlation exists.

The Brief addresses arguments which were withdrawn in view of the amendments to the claims (see page 8-9). The final rejection stated "In view of the amendments to the claims to require a blood sample, the rejection as it is drawn to particular mitochondria has been withdrawn. However, it remains unclear how the ordinary artisan would assess ATP production, for example and provide an indication of oxidative stress in an individual to obtain a measure of the amount of oxidative stress in a human individual, as required by the instant claims."

The Appellants traverse the rejection directed to the analysis of some lesions or mutations that may occur in non-coding regions and thus would not affect protein production. The Appellant asserts this is only applicable to the single mitochondria situation. This argument has been reviewed, but is not persuasive. Assuming that some mutations occurred in the coding sequence and some occurred in the non-coding sequence, it would not be predictable how mt protein production would be correlated. The skilled artisan would recognize that those changes in the non-coding regions would not likely affect the mt protein production. Thus, it is unclear how the overall pictures of mt protein production is changes and associated with oxidative stress. If the knockout's caused no protein production, it is unclear how the presence of no protein production

correlates with oxidative stress since the single mutation would knock out all production and not be an analysis of quantity of damage. Thus, turning to the claim which requires, wherein such amount of damage is indicative of oxidative stress in said individual. The amount of damage would not correlate in the same manner on the DNA level and the protein level if one mutation can knockout the entire protein function.

Response to Indefinite Arguments

The Appellant traverses the rejection. The Appellant asserts the claim has been amended to require assessing the amount. This argument has been considered but is not convincing because the claim remains drawn to a method where once the artisan has "assessed" or measured the amount of mtDNA damage the information is indicative of oxidative stress. However, the claim lacks any guidance or process step which provides the artisan how the amount or assessment is indicative of oxidative stress.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Jeanine Goldberg

Primary Patent Examiner 1634

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